# 2026 Revised Missouri Sterile Compounding Rule (20 CSR 2220-2.200) / Missouri Adoption of USP Chapter 797

Effective 7/30/2026, Board rule 20 CSR 2220-2.200 Sterile Compounding has been amended to adopt USP Chapter 797 Pharmaceutical Compounding – Sterile Preparations (2023). **Compliance with USP Chapter 797 is now required for all Class H Sterile Compounding pharmacy permit holders** *(see exceptions/allowances below)*. The Board's previous sterile compounding rule is no longer applicable and all previous references to the 2008/2013 version of USP Chapter 797 have been removed.

This guide contains an overview of major rule changes with the adoption of USP Chapter 797 in the below topic areas:

- Rule Variances
- Risk Levels vs. Compounding Categories
- Personnel Training & Evaluation
- Personal Hygiene & Garbing
- Facilities & Engineering Controls
- Microbiological Air & Surface Monitoring
- Cleaning, Disinfection & Sporicidals
- Sterilization & Depyrogenation
- Compounding Records
- Release Inspections & Testing
- Labeling
- Category 3 Compounded Sterile Preparations (CSPs)
- Recalls
- Commercially Available Products
- Quality Assurance/Quality Control

**This document is not a complete summary of all rule changes or USP Chapter 797 provisions**. 20 CSR 2220-2.200 includes additional compliance standards/requirements that are not included in this overview. Licensees should review the rule and USP Chapter 797 in their entirety to ensure compliance. In the event of a conflict between USP Chapter 797 and Missouri law/Board rules, Missouri law and board rules shall control.

Copies of USP Chapter 797 and related compendial chapters can be purchased directly from USP at: https://www.usp.org/ (a USP subscription is required). A USP subscription to just the compounding chapters is also available in the USP Compounding Compendium: https://www.usp.org/compounding/general-chapter-797.

*This document is provided for informational purposes only and does not constitute a rule statement of general applicability or binding law. This document does not constitute a comprehensive review of all compliance requirements; Other compliance requirements may exist that are not listed in this guidance. "Should," "may," and "recommend" are advisory only. In the event of a conflict or inconsistency, duly promulgated or enacted state/federal law shall control. The Board expressly reserves the right to revise the contents as deemed appropriate or necessary. Questions regarding this document can be e-mailed to MissouriBOP@pr.mo.gov.*

*Guide Note:*

- *USP Chapter 797 contains multiple requirements that will be new for Class H Sterile Compounding Pharmacies. Board compliance staff has highlighted new compliance items that are significantly different from the current rule with a new indicator flag (also italicized in red).* NEW *Not all new requirements have been highlighted; Please review the full rule for other new compliance items that are not highlighted in this document.*
- *Red flags ( ) indicate 20 CSR 2220-2.200 rule requirements that are stricter than USP Chapter 797/do not incorporate USP Chapter 797 allowances.*
- *Board compliance staff hosted three (3) webinars on the 20 CSR 2220-2.200 revisions. On-demand webinar recordings are available on the Board's website: https://pr.mo.gov/pharmacists-publications-resources.asp#videos (Recorded webinars are not eligible for pharmacist continuing education).*

## Board of Pharmacy Website

## Pharmacy Compliance Resources

## 2026 Sterile Compounding Webinars

## Rule Variances

The following sections of USP Chapter 797 are **not incorporated** into 20 CSR 2220-2.200 and are therefore not applicable to Missouri licensed pharmacies [see 20 CSR 2220-2.200(1)]:

- ***Section 1.1.2 Allergenic Extracts & Section 21 Compounding Allergenic Extracts***: The USP Chapter 797 exemption for allergenic extracts has not been adopted in Missouri.
- ***Section 1.3 Immediate-Use Compounded Sterile Preparations (CSPs)***: Pharmacies conducting sterile compounding activities that are under the Board's jurisdiction must prepare CSPs as either Category 1, 2, or 3 preparations. Preparation of CSPs under USP Chapter 797's immediate-use provision is not allowed.
- ***Compliance with USP Chapter 800 (Hazardous Drugs – Handling in Healthcare Settings)***: The Board recommends but does not require compliance with USP Chapter 800. Pharmacies that compound sterile hazardous drugs are required to establish policies and procedures which, at a minimum, include the items listed in 20 CSR 2220-2.200(1)(H).
- ***Alternative Methods***: The use of alternative technologies, techniques, materials, or procedures other than those described in USP Chapter 797, as referenced in USP Chapter 797, Section 1 (Introduction and Scope), is **prohibited** unless the alternative is validated in accordance with USP Chapter 1223 & 1225 and **approved by the Board prior to use**. Approval requests and supporting validation documentation can be e-mailed to: pharmacy@pr.mo.gov.

In addition to the above modifications, 20 CSR 2220-2.200 includes the following major variances from USP Chapter 797:

- Compounding Definition: The Board expanded USP Chapter 797's definition of compounding to also include:
  1. The docking of proprietary bag and vial systems**, and
  2. Mixing, reconstituting, or preparing an FDA-approved manufactured sterile product in accordance with the manufacturer's approved labeling recommendations [see 20 CSR 2220-2.200(1)(C)]**

***When done by a pharmacy under the Board's jurisdiction.*

Compliance with 20 CSR 2220-2.200 is required for the above compounding activities. Preparing vaccines for immediate administration is not considered sterile compounding under the Board's rule.

- 20 CSR 2220-2.400: Class H pharmacies must also comply with Board rule 20 CSR 2220-2.400 (Compounding Standards of Practice) when preparing CSPs. 20 CSR 2220-2.400 includes additional compliance requirements for compounding pharmacies that are not listed in this document.
- Compliance Responsibility: USP Chapter 797 requires assignment of a "designated person" who is responsible for sterile compounding activities. The designated person can be the pharmacist-in-charge (PIC) but is not required to be.

Identification of a designated person **does not exempt or modify any duty or responsibility of the permit holder or PIC.** The permit holder and PIC are still responsible for ensuring full compliance with the Board's rule, applicable state/federal law, and USP Chapter 797, and also ensuring compliance for any activities delegated to a designated person.

## Risk Levels vs. Compounding Categories

NEW

Prior to 7/30/2026, Board rule 20 CSR 2220-2.200 categorized sterile compounding activities by risk levels. The rule revision eliminates risk levels and instead adopts USP Chapter 797's three compounding "Categories" (Category 1, 2 & 3).

USP category levels are determined by:

- Compounding environment
- Starting ingredients
- Compounding method
- Sterility testing
- Desired beyond use date (BUD), and
- CSP storage conditions

As the CSP category increases, additional environmental controls, personnel requirements, and testing are required.

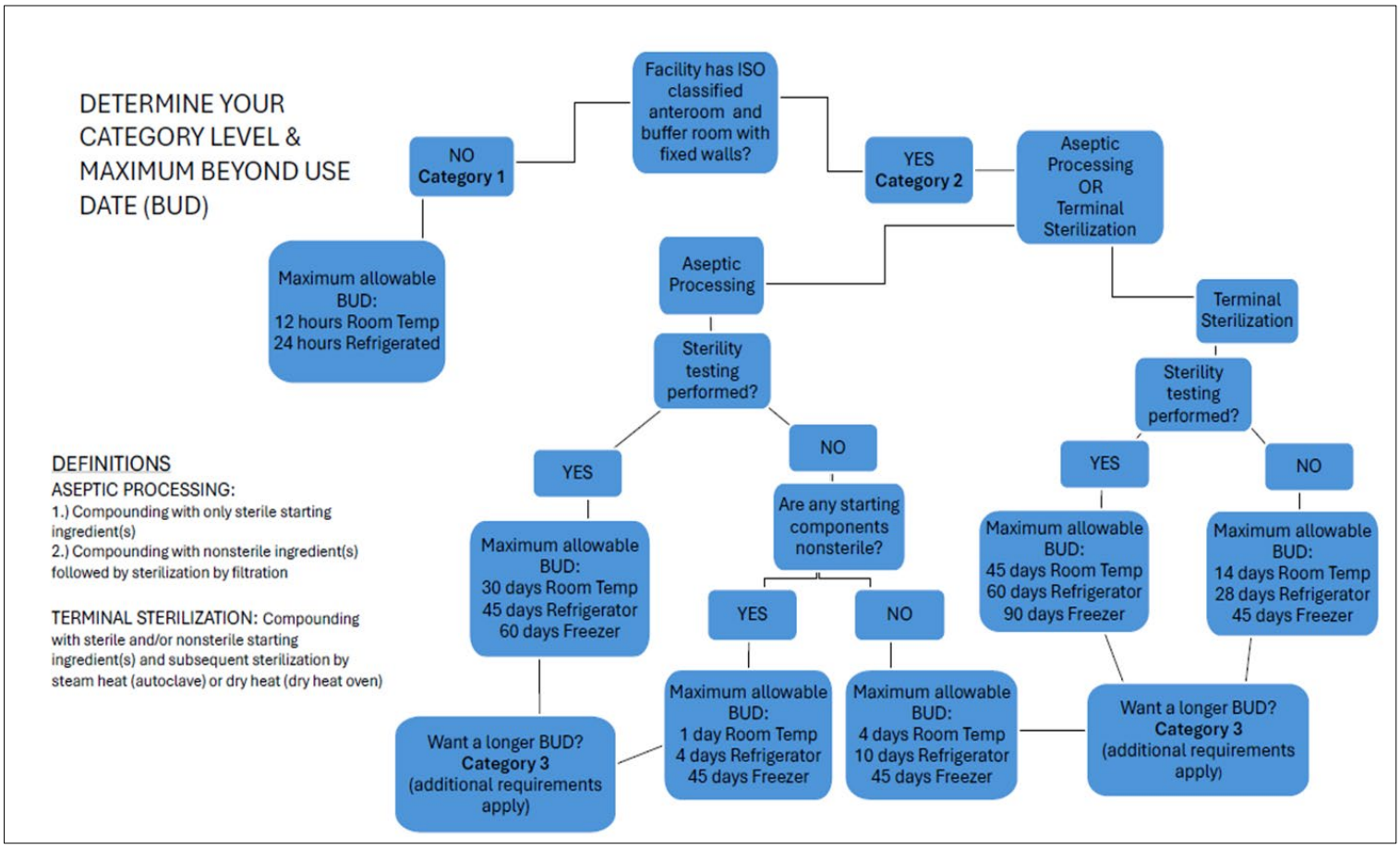
The following table provides a broad overview of the differences between "Risk levels" in previous rule 20 CSR 2220-2.200 and USP's "Categories" for CSPs. Unless otherwise specified, the USP Chapter 797 (2023) requirements apply to all CSPs:

| Risk Level Vs. Category | |
|---|---|
| *Previous 2.200* | *Revised 2.200* |
| **Risk Level 1:**<br>• Prepared with all sterile ingredients<br>• Batching or use of automated compounders not allowed<br>• Minimum compounding environment was an ISO 5 primary engineering control (PEC) located in a non-ISO classified controlled area<br>• BUD could not exceed the following:<br>– 48 hours room temp<br>– 7 days refrigerated<br>– 30 days frozen<br>• If a longer BUD was assigned, the compound was considered Risk Level 2 and risk level 2 requirements applied. | **Category 1:**<br>• CSPs can be made with nonsterile or sterile starting ingredients<br>• No limitations on batching or use of automated compounders<br>• Minimum compounding environment is an ISO 5 PEC in a non-ISO classified segregated compounding area (SCA)<br>• BUD cannot exceed the following:<br>– ≤ 12 hours room temp<br>– ≤ 24 hours refrigerated |
| **Risk Level 2:**<br>• Prepared with all sterile ingredients<br>• Batched compounds (for more than 1 patient)<br>• Preparations compounded by complex manipulations or automated compounders<br>• Minimum compounding environment was an ISO 5 PEC in an ISO 7 buffer room or a restricted access barrier (RABS) in a controlled area<br>• No maximum BUD<br>• No maximum batch sizes | **Category 2:**<br>• CSP can be made with nonsterile or sterile starting ingredients<br>• Minimum compounding environment is an ISO 5 PEC in a cleanroom suite with fixed doors and windows.<br>– Cleanroom suite must have:<br>✓ ISO 7 or 8 anteroom<br>✓ ISO 7 buffer room<br>– RABS must be in a cleanroom suite to assign Category 2 BUDs<br>• Maximum BUDs vary depending on compounding methods, starting ingredients, sterility testing, and storage conditions. (USP Chapter 797, Table 13)<br>• Exceeding BUD limits in Table 13 make the CSP a Category 3 and additional facility, personnel, environmental monitoring, and testing requirements apply.<br>• Maximum batch size of 250 units for CSPs that require sterility testing |

| Risk Level Vs. Category (Cont'd) | |
|---|---|
| *Previous 2.200* | *Revised 2.200* |
| **Risk Level 3:**<br>• Prepared with nonsterile ingredients or components<br>• Minimum compounding environment was an ISO 5 PEC in an ISO 7 buffer room OR a restricted access barrier (RABS) in a controlled area.<br>• No maximum BUD, however, potency testing required to exceed 30-day BUDs<br>• Release testing required:<br>– Sterility testing for all preps<br>– Endotoxin testing for injectables<br>• No maximum batch size | **Category 3:**<br>• CSP can be made with nonsterile or sterile starting ingredients<br>• Minimum compounding environment is an ISO 5 PEC in a cleanroom suite with fixed doors and windows.<br>– Cleanroom suite must have:<br>✓ ISO 7 or 8 anteroom<br>✓ ISO 7 buffer room<br>– RABS must be in a cleanroom suite to assign Category 3 BUDs<br>• BUDs > than Category 2 may be assigned but require additional testing such as:<br>– Stability study<br>– Container closure testing<br>– Particulate matter testing for injections or ophthalmic<br>– Sterility testing (every batch)<br>– Endotoxin testing (every batch)<br>• Maximum batch size of 250 units for Category 3 CSPs |

As identified above, the designated CSP category is largely determined by your compounding facility, the desired BUD, and your ability or willingness to conduct sterility testing. Pharmacies compounding Category 3 CSPs must always comply with Category 3 additional requirements, even if Category 3 CSPs are only prepared occasionally.

Assess your compounding procedures and use the following decision tree to assist in finding CSP categories and their corresponding BUDs:


DETERMINE YOUR CATEGORY LEVEL & MAXIMUM BEYOND USE DATE (BUD)
Facility has ISO classified anteroom and buffer room with fixed walls?
NO Category 1
YES Category 2
Maximum allowable BUD: 12 hours Room Temp 24 hours Refrigerated
Aseptic Processing OR Terminal Sterilization
Aseptic Processing
Terminal Sterilization
Sterility testing performed?
Sterility testing performed?
YES
NO
YES
NO
Maximum allowable BUD: 30 days Room Temp 45 days Refrigerator 60 days Freezer
Are any starting components nonsterile?
Maximum allowable BUD: 45 days Room Temp 60 days Refrigerator 90 days Freezer
Maximum allowable BUD: 14 days Room Temp 28 days Refrigerator 45 days Freezer
YES
NO
Want a longer BUD? Category 3 (additional requirements apply)
Maximum allowable BUD: 1 day Room Temp 4 days Refrigerator 45 days Freezer
Maximum allowable BUD: 4 days Room Temp 10 days Refrigerator 45 days Freezer
Want a longer BUD? Category 3 (additional requirements apply)
DEFINITIONS
ASEPTIC PROCESSING:
1.) Compounding with only sterile starting ingredient(s)
2.) Compounding with nonsterile ingredient(s) followed by sterilization by filtration
TERMINAL STERILIZATION: Compounding with sterile and/or nonsterile starting ingredient(s) and subsequent sterilization by steam heat (autoclave) or dry heat (dry heat oven)

The maximum BUD limits for each CSP Category are listed in USP Chapter 797, **Table 12** (Category 1), **Table 13** (Category 2) and **Table 14** (Category 3). A shorter BUD must be assigned when physical or chemical stability of the CSP is less than USP Chapter 797's provided limits.

Additionally, USP Chapter 797 provides the following for single and multiple-dose containers (both conventionally manufactured or CSPs):

- Conventionally manufactured single-dose container:
  - Once entered or punctured (in ISO 5 air), the container may be used up to 12 hours if stored according to labeling requirements
- Conventionally manufactured multiple-dose container
  - Once initially entered or punctured, the container may be used for up to 28 days (unless otherwise specified by manufacturer labeling)
- Conventionally manufactured pharmacy bulk package
  - Must be entered or punctured in an ISO 5 PEC and used according to the manufacturer's labeling

- Use of compounded single-dose CSPs and stock solutions:
  - If either are used as a component to compound additional CSPs, the original single-dose CSP or stock solution may be used for up to 12 hours after puncture. The remainder is to be discarded.
- Use of compounded multiple-dose CSPs:
  - Multiple-dose CSPs are required to pass antimicrobial effectiveness testing and meet all other requirements in Section 14.5 of USP Chapter 797. After it is entered or punctured, it can be used until the BUD or 28 days (whichever is shorter).

## Personnel Training & Evaluation

NEW

Compounding staff and those with direct oversight of compounding staff must be trained and competent to perform the duties assigned. USP Chapter 797 requires that personnel must be trained and demonstrate competency initially and every 12 months in the following topics:

- Hand hygiene
- Garbing
- Cleaning and disinfection
- Calculations, measuring, and mixing
- Aseptic technique
- Achieving and/or maintaining sterility
- Achieving apyrogenicity, if applicable
- Equipment use
- Documentation of the compounding process
- Principles of HEPA-filter unidirectional airflow in the ISO 5 area
- Proper use of PECs
- Principles of movement of materials and personnel within the compounding area

[CONTINUED ON NEXT PAGE]

Additional minimum requirements for personnel training and competency evaluations are listed below:

| Frequency and Types of Training for Compounders | | |
|---|---|---|
| *Type of Training/ Assessment* | *Previous 20 CSR 2220-2.200* | *Revised 20 CSR 2220-2.200* |
| Didactic | • Initially<br>• Content not specified<br>• Reassessment not required | • Initially & every 12 months<br>• Knowledge & competency of core skills (topics specified in USP Chapter 797) |
| Visual observation of hand hygiene and garbing | • Initially<br>• Risk level 1 & 2: every 12 months<br>• Risk level 3: every 6 months | • Initially (x 3)<br>• Category 1 & 2: every 6 months<br>• Category 3: every 3 months |
| NEW Post-garb gloved fingertip and thumb sampling (GFT) | • Not required | • Initially (x 3)<br>• Category 1 & 2: every 6 months<br>• Category 3: every 3 months |
| Visual observation of aseptic technique | • Initially<br>• Risk level 1 & 2: every 12 months<br>• Risk level 3: every 6 months | • Initially<br>• Category 1 & 2: every 6 months<br>• Category 3: every 3 months |
| Media-fill test | • Initially (x3)<br>• Risk level 1 & 2: every 12 months<br>• Risk level 3: every 6 months | • Initially *(no longer required to do 3 media-fill tests)*<br>• Category 1 & 2: every 6 months<br>• Category 3: every 3 months |
| NEW Post-compounding GFT (sample taken at end of media-fill test) | • Not required | • Initially<br>• Category 1 & 2: every 6 months<br>• Category 3: every 3 months |
| NEW Post-compounding surface sample of PEC (sample taken at end of media-fill test) | • Not required | • Initially<br>• Category 1 & 2: every 6 months<br>• Category 3: every 3 months |

NEW USP Chapter 797 also requires the following training for personnel with direct oversight of compounding:**

| *Frequency & Type for Personnel with Direct Oversight of Compounding* | |
|---|---|
| *Type of Training/Assessment* | *Revised 20 CSR 2220-2.200* |
| Didactic | • Initially & every 12 months<br>• Knowledge & competency of core skills (topics specified in USP Chapter 797) |
| Visual observation of hand hygiene and garbing | • Initially (x 3)<br>• Every 12 months |
| Post-garb gloved fingertip and thumb sampling (GFT) | • Initially (x 3)<br>• Every 12 months |
| Visual observation of aseptic technique | • Initially & Every 12 months |
| Media-fill test | • Initially & Every 12 months |
| Post-compounding GFT (sample taken at end of media-fill test) | • Initially & Every 12 months |
| Post-compounding surface sample (sample taken of direct compounding area at end of media-fill test) | • Initially & Every 12 months |

*****Personnel with direct oversight of compounding activities must complete all compounder evaluations if the individual compounds.***

## Hand Hygiene & Garbing Competency

NEW Prior to compounding or having direct oversight of compounding activities, personnel must complete an initial garbing competency evaluation. The evaluation must include:

- Visual observation of procedures
- Gloved fingertip and thumb sampling (GFT) of both hands:
  - Samples must be collected after garbing, before applying sterile alcohol
  - One media device required per hand
  - Samples must be collected in classified area or SCA
- Initial evaluation must be completed three times (x3), in succession. Each evaluation must assess a separate, complete hand hygiene and garbing procedure.

Reassessment evaluations must include/be completed as follows:

- Visual observation of procedures
- GFT sampling of both hands; Collected after garbing
  - Compounders: Every 6 months (Category 1 & 2); Every 3 months (Category 3)
  - Personnel with direct oversight of compounders: Every 12 months

The reassessment evaluation must consist of one (1) visual observation and one (1) GFT sampling (of both hands). A triplicate evaluation is not required for the ongoing evaluation.

## Aseptic Manipulation Competency Evaluations

Prior to compounding or having direct oversight of compounding activities, personnel must complete an aseptic manipulation competency evaluation that includes:

- A visual observation of aseptic technique
- Media-fill testing
- NEW Gloved fingertip sampling (collected at end of media-fill test), and
- Surface sampling of the direct compounding area (collected at end of media-fill test)

NEW The initial evaluation no longer requires the media-fill test to be done in triplicate.

Reassessment evaluations must be completed as follows:

- Compounders: Every 6 months (Category 1 & 2); Every 3 months (Category 3)
- Personnel with direct oversight of compounders: Every 12 months

## Media-fill Tests

Media-fill tests must simulate the most difficult and challenging compounding procedures. The simulation must capture the following elements of the procedure(s):

- Factors associated with the length of the process (operator fatigue or quality of equipment)
- Number of aseptic additions or transfers
- Number, type, and complexity of manipulations, and
- Number of personnel in the buffer room or SCA

NEW Immediately following the media-fill test:

- GFT samples must be collected from both hands while inside the PEC
- Surface samples must be collected of direct compounding area in PEC

*****GFT and surface samples must be collected prior to disinfecting gloves or the PEC.***

## Types of Media & Incubation

All samples must be incubated in an incubator and inverted when applicable. Allowed media used for GFT samples & surface samples are:

- Trypticase soy agar (TSA) with neutralizing additives (e.g., lecithin and polysorbate 80)
- Incubation parameters: 30-35°C for at least 48 hours, followed by 20-25°C for an additional 5 days.

The following media are allowed for media-fill tests:

- Soybean-casein digest (aka TSB)
  - If all starting components are sterile, **sterile media** must be used for media-fill testing. A certificate of analysis with growth promotion must be obtained from the media supplier.
  - If some components are nonsterile, **nonsterile media** must be used. Prepare at least 1 container as the positive control for growth promotion.
- Incubation parameters: 20-25°C and 30-35°C for a minimum of 7 days each

## Documentation

Compliance with USP Chapter 797's personnel & other competency training/evaluations must be maintained in the pharmacy's records. At a minimum, documentation of garbing and aseptic manipulation evaluations must include:

- Name of person evaluated
- Evaluation date and time
- Media and components used including, but not limited to, manufacturer, expiration date, and lot number
- Starting temperature for each incubation interval
- Incubation dates
- Evaluation results, and
- Identification of observer and person reading and documenting results.

## Competency Evaluation Failures

Aseptic manipulation and competency assessments must be thoroughly and adequately conducted, to ensure safe compounding practices. As per USP Chapter 797, the following criteria constitute a failure of the required competency evaluations:

- Garbing & Hand Hygiene Competency Failure: Visual observation of improper procedures or GFT results that exceed action levels

| Action Levels for Gloved Fingertip Sampling | |
|---|---|
| *Gloved Fingertip and Thumb Sampling* | *Action Levels (CFU *, Total from both hands)* |
| After garbing | >0 |
| After media-fill testing | >3 |

**Colony forming units*

- Media-fill test failure: Visible turbidity or other visual manifestations of growth in any container
- Surface sample failure: Action levels exceed the following:

| Action Levels for PEC Surface Sampling | |
|---|---|
| *ISO Class* | *Action Levels (CFU/Media Device)* |
| 5 | >3 |

**A failure in either the media-fill test, GFT sampling, or surface sample is an overall failure of the aseptic manipulation competency evaluation.**

The following actions must be taken in the event an individual fails a required competency evaluation:

- Investigate the potential cause of the failure
- Take corrective actions (e.g., additional training). Corrective actions must be taken prior to the individual resuming compounding and documented
- Repeat the evaluation, as required by USP Chapter 797.

## Transferring Staff Competency Evaluations:

20 CSR 2220-2.200(2)(B) allows competency evaluation results for an individual to be transferred between facilities under common ownership or control if:

- The aseptic manipulation competency evaluation captures the most difficult and challenging conditions the individual will be performing and was completed within USP Chapter 797's required time frames
- Pharmacies accepting transferred competency evaluation results must maintain current and written policies and procedures governing the transfer of results, and
- The individual is trained in applicable procedures or duties, including procedures/duties that differ from the pharmacy that conducted the initial evaluation.

In the event of an emergency, a pharmacy may accept the required competency evaluation from a pharmacy or hospital that is not under common ownership or control, however:

- A pharmacist must verify that the evaluation complies with USP Chapter 797 and maintain documentation of the required competency evaluation with the dates and results
- The individual with transferred results must be trained in applicable procedures specific to the pharmacy as needed to ensure proper compounding, and
- The receiving pharmacy must maintain a manual or electronic copy of the other pharmacy's or hospital's policies and procedures. [20 CSR 2220-2.200(2)(C)]

Individuals with transferred competency evaluation results under the emergency allowance may assist with compounding for up to **forty-five (45) days**. [20 CSR 2220-2.200(2)(C)] After 45 days, the individual must complete the required competency evaluations at that specific pharmacy location.

## Personal Hygiene & Garbing

NEW Minimum hygiene & garbing requirements have changed to match USP Chapter 797. See charts below for a direct comparison:

### Previous 2.200

| Risk level 1 | Risk level 2 & 3 |
|---|---|
| •Non-shedding gown<br>•Hair & beard cover<br>•Face mask<br>•Gloves (sterile not required)<br>•Shoe covers not required | •Non-shedding gown<br>•Hair & beard cover<br>•Face mask<br>•Sterile gloves<br>•Shoe covers |

### Revised 2.200

| Category 1 & 2 | Category 3 |
|---|---|
| •Low-lint gown<br>•Low-lint hair & beard cover<br>•Low-lint face mask<br>•Sterile gloves<br>•Low-lint shoe covers | •Same garb as Category 1 & 2 but it must all be sterile<br>•No exposed skin<br>•Face and neck covered |

Revised 20 CSR 2220-2.200 also includes the following hand hygiene & garbing differences:

| *Hand Hygiene & Garbing Differences* | | |
|---|---|---|
| | *Previous 20 CSR 2220-2.200* | *Revised 20 CSR 2220-2.200* |
| Hand Hygiene | • Remove debris from underneath fingernails<br>• Wash hands and forearms for 30 seconds | • Clean under fingernails with disposable nail cleaner<br>• Wash hands and forearms for 30 seconds<br>• Brushes not allowed<br>• Hand dryers not allowed<br>• Disposable soap containers cannot be refilled |
| NEW Hand-rub | • Recommended but not required | • Alcohol-based hand rub must be used before donning sterile gloves<br>• Alcohol-based hand rub must also be used prior to donning garb if hand hygiene is completed outside of a classified area |
| Eyeglasses | ____ | • Eyeglasses must be wiped before entering compounding area |

| *Hand Hygiene & Garbing Differences (Cont'd)* | | |
|---|---|---|
| | *Previous 20 CSR 2220-2.200* | *Revised 20 CSR 2220-2.200* |
| Garb storage | Not Specified | • Garb must be stored to minimize contamination (e.g., away from sinks to avoid splashing) |
| Re-use of garb | Not specified | • Garb must be discarded and cannot be reused when personnel exit the compounding area (excluding gowns)<br>• Gowns may be reused within the same shift |

*** The order of hand hygiene and garbing depends on the placement of the sink.*

20 CSR 2220-2.200's garbing requirements for RABS are stricter than USP Chapter 797. Specifically:

- RABS sleeves and gloves must be changed per manufacturer's recommendations
- Disposable gloves must be worn inside the gloves attached to the RABS sleeves, &
- Sterile gloves must be worn over the gloves attached to the RABS sleeve. [20 CSR 2220-2.200(4)]

## Facilities & Engineering Controls

The compounding environment plays a significant role in determining which categories of CSPs may be prepared and, ultimately, the BUDs that can be assigned. See the chart below for a comparison of minimum facility requirements:

| *Minimum Facility Requirements* | | |
|---|---|---|
| *Facility Configuration* | *Previous*<br>*20 CSR 2220-2.200* | *Revised*<br>*20 CSR 2220-2.200* |
| Laminar airflow workbench (LAFW) or biological safety cabinet (BSC) in a non-ISO classified controlled area | <u>Allowed to:</u><br>• Conduct Risk Level 1 compounding<br>• Assign BUD up to: 48 hours room temp; 7 days refrigerated; 30 days freezer<br><br><u>Restrictions:</u><br>• No batching (compounding multiple CSPs intended for more than 1 patient)<br>• No automated compounding devices<br>• No preparing a CSP with complex manipulations<br>• No compounding with nonsterile ingredients or components<br><br>***Rule no longer effective** | <u>Allowed to:</u><br>• Compound Category 1 CSPs Assign BUD up to: 12 hours room temp; 24 hours refrigerated<br>• Batch CSPs<br>• Use automated compounding devices<br>• Prepare a CSP with complex manipulations<br>• Compound using nonsterile ingredients or components<br><br><u>Restrictions:</u><br>• Cannot assign a BUD greater than 12 hours room temp; 24 hours refrigerated<br>• Cannot freeze Category 1 CSPs |
| RABS including compounding aseptic isolator (CAI) or compounding aseptic containment isolator (CACI) in a non-ISO classified area | <u>Allowed to:</u><br>• Conduct risk level 1, 2, or 3 compounding<br>• Assign BUDs greater than: 48 hours room temp; 7 days refrigerated; 30 days freezer<br><br><u>Restrictions:</u><br>• No restrictions on BUDs or compounding activities<br><br>***Rule no longer effective** | <u>Allowed to:</u><br>• Compound Category 1 CSPs<br>• Assign BUD up to: 12 hours room temp; 24 hours refrigerated<br>• Batch CSPs<br>• Use automated compounding devices<br>• Prepare a CSP with complex manipulations<br>• Compound using nonsterile ingredients or components<br><br><u>Restrictions:</u><br>• Cannot assign a BUD greater than 12 hours room temp; 24 hours refrigerated<br>• Cannot freeze Category 1 CSPs |

| *Minimum Facility Requirements (Cont'd)* | | |
|---|---|---|
| *Facility Configuration* | *Previous*<br>*20 CSR 2220-2.200* | *Revised*<br>*20 CSR 2220-2.200* |
| LAFW or BSC or RABS in an ISO 7 classified buffer room | Allowed to:<br>• Conduct risk level 2 or 3 compounding<br>• Batch CSPs (no maximum batch size)<br>• Use automated compounding devices<br>• Prepare a CSP with complex manipulations<br>• Compound using nonsterile ingredients or components<br>• Have plastic curtain partitions as walls/doors in buffer room<br>• Operate without an anteroom<br>• Operate without minimum pressure differentials or air changes per hour (ACPH)<br>• Assign BUDs greater than: 48 hours room temp; 7 days refrigerated; 30 days freezer<br><br>Restrictions:<br>• Risk level 3 CSPs limited to a 30-day BUD; Option to extend risk level 3 BUD with potency testing<br><br>***Rule no longer effective*** | If you have an ISO 7 buffer room but **do not** have an anteroom, fixed doors/walls, minimum pressure differentials, or minimum ACPH, then you are allowed to:<br>• Compound Category 1 CSPs<br>• Assign BUD up to: 12 hours room temp; 24 hours refrigerated<br>• Batch CSPs<br>• Use automated compounding devices<br>• Prepare a CSP with complex manipulations<br>• Compound using nonsterile ingredients or components<br><br>Restrictions:<br>• Cannot assign a BUD greater than 12 hours room temp; 24 hours refrigerated<br>• Cannot freeze Category 1 CSPs<br><br>If you have a cleanroom suite **with** an ISO 7/8 anteroom, ISO 7 buffer room, fixed walls/doors, minimum pressure differentials, and minimum ACPH, then you are allowed to:<br>• Compound Category 1, 2, or 3 CSPs<br>• Assign BUD greater than: 12 hours room temp; 24 hours refrigerated<br><br>Restrictions include:<br>• Must adhere to maximum BUDs dependent upon your compounding methods, sterility testing, starting ingredients, and storage conditions<br>• Cannot extend BUDs past the limits established for Category 2 or 3 (Tables 13 & 14 in USP 797)<br>• Maximum batch size of 250 units for CSPs that require sterility testing |

## Cleanroom Suites

To compound Category 2 & 3 CSPs, and assign BUDs greater than 12 hours room temperature or 24 hours refrigerated, a cleanroom suite is required with the following:

- ISO 7 or ISO 8 anteroom with a line of demarcation (LOD). **May have 2 separate anterooms, in lieu of LOD.*
- ISO 7 buffer room
- Temperature & humidity monitors
- Fixed walls/doors
- Pressure differential monitoring system
- Air supply through ceiling HEPA filters
- Surfaces must be smooth, impervious, free from cracks and crevices, and non-shedding
- Low air returns or smoke study showing absence of stagnant air
- Minimum ACPH as follows:
  - 30 ACPH for ISO 7 rooms
  - 20 ACPH for ISO 8 rooms
- For both rooms, at least 15 ACPH must come from ceiling HEPA filters
- Minimum differential positive pressure of 0.020-inch water column between:
  - Buffer room and anteroom
  - Anteroom and unclassified area(s)
- Junctures between the ceiling and walls and between the walls and floors must be sealed
- Ceiling panels must be caulked if inlaid panels
- Walls constructed of or covered with durable material to maintain surface integrity
- Floors must have coving to sidewall or floor/wall junctures must be caulked
- Dust-collecting overhangs must be minimized (e.g., utility pipes, ledges, windowsills) *(Requirement is stricter than USP Chapter 797.)*

## Segregated Compounding Areas (SCA)

SCAs must comply with the following:

- SCAs may be located in an unclassified area, however, the SCA "must be located away from unsealed windows, doors that connect to the outdoors, and traffic flow", as per USP Chapter 797. **The area must be defined with a visible perimeter (door, walls, or visible floor marking).
- Surfaces must be clean, uncluttered, and dedicated to compounding.
- Dust-collecting overhangs must be minimized, such as utility pipes, ledges, and windowsills. **20 CSR 2220-2.200(3)(C); Stricter than USP Chapter 797*
- The area within one (1) meter of the PEC must be dedicated only for sterile compounding (e.g., not storage, hand hygiene, donning and doffing garb, patient care, or other highly particle-generating activities). **20 CSR 2220-2.200(3)(D); Stricter than USP Chapter 797*

## Sink Placement

Previous rule 20 CSR 2220-2.200 provided a sink with hot and cold must be near, but not in, the controlled or buffer area. USP Chapter 797 modifies this requirement as listed below based on location:

- **Facilities with a Cleanroom Suite:**
  - Sink used for hand hygiene may be placed inside or outside of anteroom.
  - If sink is outside of the anteroom, it must be located in a clean space.
  - If the sink is inside the anteroom, it may be placed on either the clean or dirty side of the anteroom.
- **Facilities with an SCA**
  - May be either inside the SCA or in close proximity to the SCA
  - Hand washing sink must be placed at least 1 meter away from the PEC.

## Prohibited Items (Classified Areas/SCAs)

USP Chapter 797 provides items that may impact environmental quality or do not promote effective cleaning & disinfection are not allowed in SCAs and/or classified areas. Examples of other prohibited items include, but are not limited to:

| *Prohibited Items* | |
|---|---|
| *SCA* | *Classified Areas* |
| • Free standing air conditioners, humidifiers, dehumidifiers<br>• Shipping cartons, corrugated or uncoated cardboard<br>• Food, mints, gum, drinks<br>• Cosmetics<br>• Hand, wrist, and other exposed jewelry. (cover any jewelry that cannot be removed)<br>• Electronic devices that are not necessary for compounding or other required tasks<br>• Nail products (nail polish, artificial nails, extenders)<br>• Furniture, supplies, equipment or materials not necessary for compounding | • Free standing air conditioners, humidifiers, dehumidifiers<br>• Tacky mats<br>• In the buffer room: plumbed water sources such as sink, eyewashes, showers, or floor drains<br>• In the anteroom: floor drains<br>• Shipping cartons, corrugated or uncoated cardboard<br>• Food, mints, gum, drinks<br>• Cosmetics<br>• Hand, wrist, and other exposed jewelry. (cover any jewelry that cannot be removed)<br>• Electronic devices that are not necessary for compounding or other required tasks<br>• Nail products (nail polish, artificial nails, extenders)<br>• Furniture, supplies, equipment or materials not necessary for compounding |

Inspectors continue to see signs of equipment damage, decay, rust, and corrosion in SCAs and cleanroom suites. Therefore, revised 20 CSR 2220-2.200(3)(C) provides Class H pharmacies must include the following in their policies/procedures, in addition to USP Chapter 797 requirements:

- Selecting, handling, and monitoring of cleaning, disinfecting, and sporicidal agents to prevent/minimize equipment damage and decay, and
- Inspecting the PECs, cleanroom suite, SCA, and equipment and correcting/repairing any damage, rust, or corrosion.

## Board Waivers

Rule 20 CSR 2220-2.200 is currently effective and mandatory for all Class H pharmacies. However, Class H pharmacies that are licensed on 7/30/2026, may petition the Board for a waiver of USP Chapter 797's facility and equipment requirements if immediate compliance with revised 20 CSR 2220-2.200 cannot be completed despite due diligence or would result in undue hardship or adversely impact patient care.

**This exemption is only applicable to facility and equipment requirements!** Waiver requests may be submitted via mail or e-mailed to pharmacy@pr.mo.gov for Board review *(e-mail is preferred)*. **Include the specific requirements/items you are asking the Board to waive and an estimated timeline for completion/compliance.

Approved waivers may be granted for a limited time-period designated by the Board but **cannot extend past 7/30/2028**.

## Certification of Primary & Secondary Engineering Controls

The required frequency of certification for primary and secondary engineering controls remains unchanged from the previous 20 CSR 2220-2.200 requirements:

- Initially
- Every 6 months

Recertification is required in the following circumstances:

- Changes to the classified area(s), including redesign, construction, or reconfiguration of the room that could affect airflow or quality, or
- PECs are replaced or relocated.

Revised 20 CSR 2220-2.200 adopts USP Chapter 797 requirement that the following minimum tests must be included with certifications (new items *italicized in red*):

- Airflow testing:
  - Purpose: Ensures consistent airflow and appropriate air quality is maintained under dynamic operating conditions
  - NEW Includes air velocity, *room air exchange rate (ACPH), and room pressure differentials.*

- HEPA filter integrity testing
  - Purpose: Identifies leaks in the HEPA filter(s)
  - Must be leak tested at the factory, after installation, and as part of recertification
- Total particle count testing
  - Purpose: Confirms levels of total airborne particles are within acceptable limits (ISO Class)
  - Must be conducted under dynamic conditions
- NEW *Dynamic airflow smoke pattern test of PEC*
  - Purpose: Demonstrates the PEC is providing unidirectional airflow under dynamic conditions

Written or electronic documentation must be kept demonstrating compliance. Certification results must be reviewed by the designated person; The reviewer must confirm that all required tests were performed and were within specification. Review documentation must be maintained with the reviewer's name and date of review.

In addition to test results, USP Chapter 797 provides the following information must also be documented in the certification report:

- Total ACPH, with the number of ACPH from the HVAC and the PEC
- The number of personnel present in each PEC and ISO classified room(s) during total particle count testing and dynamic airflow-smoke pattern tests

Deficiencies or failures that may impact preparation sterility or quality must be investigated and corrected prior to further compounding.

- As specified in USP Chapter 797, Section 5, a "corrective action plan must be implemented and documented in response to any out-of-range results. Data collected in response to corrective actions must be reviewed to confirm the actions taken have been effective."
- Examples of corrective action may include (but are not limited to):
  - Process or facility improvements
  - HEPA filter replacement/repair
  - Recertification.

## Microbiological Air and Surface Monitoring

Also known as environmental monitoring or viable sampling, a microbiological air and surface monitoring program provides information on the environmental quality of the compounding area. Primary engineering controls, cleanroom suites and SCAs are not sterile, however, implementing appropriate standards/controls will help reduce levels of microorganisms in compounding areas (e.g., proper personnel practices, cleaning and disinfecting, engineering controls)

It is imperative that pharmacies sample primary engineering controls, cleanroom suites and SCAs to collect information and verify that your practices are effective at reducing airborne and surface contaminants and maintaining sterility. Data collection as part of a comprehensive monitoring program will allow the pharmacy to establish a bio-burden baseline, trend patterns, identify potential routes of contamination, and can help identify/implement needed corrective action to minimize the risk of CSP contamination.

The following chart outlines differences in routine viable air and surface sampling frequencies with the rule change:

| *Microbiological Air Monitoring* | |
|---|---|
| *Previous 2.200* | *Revised 2.200* |
| **Risk Level 1, 2, & 3:**<br>• Air sampling of all ISO classified areas before initial compounding and then every 6 months | **Category 1 & 2:**<br>• Air sampling of all ISO classified areas before initial compounding and then every 6 months<br><br>**Category 3:**<br>• Air sampling of all ISO classified areas within 30 days prior to beginning to mix any Category 3 CSP, and at least monthly thereafter |
| *Microbiological Surface Monitoring* | |
| *Previous 2.200* | *Revised 2.200* |
| **Risk Level 1:**<br>• No requirement for surface sampling<br><br>**Risk Level 2:**<br>• Surface sampling of all ISO classified areas every 6 months<br><br>**Risk Level 3:**<br>• Surface sampling of all ISO classified areas every 30 days | **Category 1 & 2:**<br>• Surface sampling of all ISO classified areas and pass-through chambers connecting to classified areas at least monthly NEW<br><br>**Category 3:**<br>• Surface sampling of all ISO classified areas and pass-through chambers connecting to classified areas prior to assigning a Category 3 BUD and at least weekly thereafter.<br>  ○ Weekly surface sampling must be done regardless of the frequency of compounding Category 3 CSPs<br>• PECs used to prepare Category 3 CSPs must also be sampled at the end of each batch (before cleaning/disinfection occurs) |

In addition to the routine sampling frequencies described above, sampling must also be performed in the following circumstances:

- In conjunction with the certification of new facilities and equipment
- After any servicing of facilities or equipment
- In response to identified problems (e.g., positive growth in sterility tests of CSPs)
- In response to identified trends (e.g., repeated positive GFT results, failed media-fill testing, or repeated observations of air or surface contamination), or
- In response to changes that could impact the sterile compounding environment (e.g., change in cleaning agents).

Additional minimum requirements include:

- The monitoring program must be clearly described in writing and include:
  - A diagram of the sampling locations
  - Procedures for collecting samples
  - Sampling frequency
  - Required sample sizes (e.g., surface area, volume of air)
  - Time of day sampling conducted in relation to activities in the compounding area, and
  - Action levels that will trigger corrective action
- NEW All air and surface monitoring results must be reviewed by the designated person, as defined by USP Chapter 797. [20 CSR 2220-2.200(7)] The reviewer's name and review date must be documented in the pharmacy's records.
- For air sampling:
  - Sampling must be conducted in all classified areas during dynamic operating conditions
  - Samples must be collected by a volumetric impaction air sampler. Settling plates are not an appropriate method of testing
  - At least 1 cubic meter or 1000 L of air must be tested from each location
  - A general microbiological growth media (e.g., TSA) must be used and must have a Certificate of Analysis (COA) from the manufacturer
  - Samples must be incubated at 30°-35°C for at least 48 hours followed by 20°-25°C for at least 5 days
- For surface sampling:
  - Routine surface sampling must be conducted at the end of a compounding activity or shift but **before the area has been cleaned and disinfected** **20 CSR 2220-2.200(7)*; *Stricter than USP Chapter 797.*
  - Sampling must be conducted in each classified area and any pass-through chambers that connect to classified areas. Locations must be selected using a risk-based approach
  - A general microbiological growth media (e.g., TSA) supplemented with neutralizing additives (e.g., lecithin and polysorbate 80) must be used; Growth media must be accompanied by a COA from the manufacturer.

- Media devices must have a raised convex surface. See USP Chapter 797, Section 6.3.2. for alternative methods for irregular surfaces and hard to reach locations.
- After sampling, the sampled area must be cleaned and disinfected
- Samples must be incubated at 30°-35°C for at least 48 hours followed by 20°-25°C for at least 5 days

## Action Levels and Remedial Investigations

A remedial investigation is required if any environmental monitoring sample demonstrates a colony forming unit (CFU) count that exceeds USP Chapter 797's recommended action levels for the type of sampling (see below). The remedial investigation must be documented in the pharmacy's records and include resampling of all affected areas to ensure a suitable state of microbial control.

A remedial investigation is required if the CFUs exceed the following thresholds:

| ISO Class | Air Sampling (CFU/cubic meter (1000 liters) of air/media device) | Surface Sampling (CFU/media device) |
|---|---|---|
| 5 | >1 CFU/$m^3$ | >3 CFU |
| 7 | >10 CFU/$m^3$ | >5 CFU |
| 8 | >100 CFU/$m^3$ | >50 CFU |

NEW Action levels remain mostly unchanged with the amended rule. The only change is a decreased action level for ISO Class 8 surface samples (from 100 CFU to 50 CFU).

Remedial investigation requirements also remain mostly unchanged with the amended rule. At a minimum, remedial investigations must include the following:

- NEW An attempt to identify recovered microorganisms *to the genus level* (when the action level is exceeded)
- An investigation into the cause of the exceeded action level
- Corrective action(s): The required action will depend on facility conditions, the CFU count, and the recovered microorganism(s). Examples of potential corrective actions include, but are not limited to, process/facility improvements, training/retraining of facility staff, cleaning and disinfecting, or HEPA filter repair/replacement.
- Resampling to confirm the corrective action was effective. If the resample exceeds action levels, pharmacies must notify the Board within three (3) business days. [20 CSR 2220-2.200(8)(C)] Notification should be e-mailed to: MissouriBOP@pr.mo.gov
- Documentation of the investigation and corrective action(s).

20 CSR 2220-2.200(8)(A) requires that pharmacies cease compounding during remedial investigations. However, 20 CSR 2220-2.200(8)(B) provides a pharmacy may continue compounding if the pharmacy reduces the BUDs and cleans as indicated in the below chart:

| *Requirements to Continue Compounding During a Remedial Investigation* | | | |
|---|---|---|---|
| *Site exceeding action levels* | *Cleaning/Disinfection* | *BUD Reduction* | *Resampling Requirements* |
| **ISO 5 PEC** | Clean and disinfect with EPA registered *sterile* cleaning, disinfecting, and sporicidal agents (or combination product), followed by sterile IPA | Assigned BUD cannot exceed 12 hours | • Resample under dynamic conditions<br>• If resampling exceeds action levels, compounding must cease until resampling shows a suitable state of microbial control has been achieved in the PEC, unless otherwise authorized by the Board. |
| **ISO 7 Buffer Room** | Clean and disinfect with EPA registered cleaning, disinfecting, and sporicidal agents (or combination product) | Assigned BUD cannot exceed 24 hours | • Resample under dynamic conditions<br>• If two consecutive resamplings exceed action levels, compounding must cease until resampling shows a suitable state of microbial control has been achieved in the affected room, unless otherwise authorized by the Board |

## Cleaning, Disinfection & Sporicidals

NEW

USP Chapter 797, Section 7 *(Cleaning, Disinfecting, and Applying Sporicidal Disinfectants and Sterile 70% IPA)*, contains detailed requirements that are applicable to all Class H pharmacies. The most notable changes to cleaning and disinfection include the requirement that all agents and supplies used in ISO 5 PECs must be **sterile** (including cleaners, disinfectants, sporicidals, wipers, mop heads), and the requirement that pharmacies incorporate use of a **sporicidal agent** in all classified areas.

| *Frequency of Cleaning and Disinfection* | | | |
|---|---|---|---|
| *Site* | *Previous 2.200* | *Revised 2.200* | |
| | | *Cleaning/Disinfecting* | *Sporicidal Use* |
| **ISO Class 5 PEC** | • Daily cleaning: Germicidal cleaning agent followed by sterile alcohol<br>• Frequent disinfection throughout the day using sterile alcohol (includes prior to compounding, between batches and after spills/surface contamination) | • Daily; followed by sterile 70% IPA for residue removal<br>• Sterile 70% IPA application:<br>– Immediately before initiating compounding<br>– Every 30 minutes. If compounding process is >30 minutes, continue compounding and disinfect immediately after compounding | • Monthly: Category 1 and 2 CSPs<br>• Weekly: Category 3 CSP |
| **Removable work tray of the PEC (when applicable)** | • Not specified | • Daily: Work tray surface<br>• Monthly: Areas underneath work tray | • Monthly: Work tray surfaces and areas underneath |
| **Equipment outside the PEC(s)** | • Not specified | • Daily | • Monthly |
| **Ceilings** | • Monthly | • Monthly | • Monthly |
| **Sink** | • Not specified | • Daily | • Monthly |
| **Counters and work surfaces Floors** | • Daily | • Daily | • Monthly: Category 1 & 2 CSPs<br>• Weekly: Category 3 |
| **Floors** | • Daily | • Daily | • Monthly: Category 1 & 2 CSPs<br>• Weekly: Category 3 |
| **Pass-through chambers** | • Daily | • Daily | • Monthly: Category 1 & 2 CSPs<br>• Weekly: Category 3 |
| **Walls, doors, door frames** | • Monthly | • Monthly | • Monthly |
| **Storage shelving and bins** | • Monthly | • Monthly | • Monthly |

## Sterilization & Depyrogenation

Revised 20 CSR 2220-2.200 incorporates USP Chapter 797's sterilization and depyrogenation requirements, including the requirement that Class H pharmacies verify the effectiveness of cycles. A general summary is provided below:

## Sterilization

CSPs prepared from one or more nonsterile components or nonsterile supplies or devices, must be sterilized. The sterilization method used must sterilize the CSP without degrading its physical and chemical stability or the packaging integrity. Terminal sterilization (e.g., steam or dry heat) is the preferred method unless the CSP or container closure system cannot tolerate it.

NEW

As per USP Chapter 797, injectable compounded preparations that contain nonsterile components or come into contact with nonsterile devices during the compounding procedure must be sterilized **within 6 hours**.

## Sterilization by Filtration

Sterilization by filtration is considered aseptic processing and is accomplished by using a filter with a pore size of 0.22 µm or smaller. The sterilizing filter must have the following characteristics:

- Sterile
- Depyrogenated
- Pore size of 0.22 µm or smaller
- Appropriate for pharmaceutical use. **Filters designated as "for laboratory or research use only" are not appropriate**
- Certified by the manufacturer to retain at least $10^7$ microorganisms of *Brevundimonas diminuta* per square centimeter of upstream filter surface area (this information is usually on the filter COA)
- Be chemically and physically compatible with the CSP
- Be chemically stable at the pressures and temperatures that will be used
- Capacity to filter the required volume, and
- Capable of undergoing filter integrity testing.

All filter units used to sterilize CSPs must undergo the manufacturers' recommended integrity testing (e.g., post-use bubble point test).

In the event a filter fails an integrity test, all CSPs prepared using the filter must either be discarded or refiltered after investigating the cause of the failure (cannot be refiltered more than one additional time).

## Sterilization by Steam Heat

Sterilization by steam heat is considered terminal sterilization and is accomplished by using saturated steam under pressure (e.g., autoclaving). According to USP Chapter 797, this is "the preferred method for terminal sterilization of aqueous CSPs in their final, sealed container closure system."

All materials must be directly exposed to steam under adequate pressure and time. The applicable temperature, pressure, and time can vary, but a typical cycle is 121° saturated steam under a pressure of 15psi for 20-60 minutes.

Procedures must be developed to minimize the risk of post-sterilization microbial contamination for supplies or equipment (e.g., wrapping of items, using envelopes that allow steam penetration). Sealed containers (e.g., stoppered and crimped empty vials) must contain a small amount of sterile water in them to generate steam.

NEW If a CSP is undergoing steam sterilization, the solution must be filtered with at least a 1.2 µm filter before going into its final container to remove particulate matter. Effectiveness of the steam sterilization must be verified with each sterilization run by using biological indicators.

The date, run, and load numbers of the steam sterilizer used for CSPs must be documented in the pharmacy's compounding record.

## Sterilization by Dry Heat

Dry heat sterilization is used for items that cannot undergo steam sterilization or when moisture would damage the material or if the wrapping materials are impermeable. To achieve sterilization by dry heat, the temperatures and exposure time are higher than steam sterilization.

NEW If a CSP is undergoing sterilization by dry heat, the solution must be filtered with at least a 1.2 µm filter before going into its final container to remove particulate matter. Effectiveness of dry heat sterilization must be verified with each sterilization run by using biological indicators and other confirmation methods (temperature-sensing devices).

The date, run, and load numbers of the dry heat oven used for CSPs must be documented in the pharmacy's compounding record.

***See USP Chapter 1229 for additional information on sterilization via filtration, steam heat or dry heat.*

## Depyrogenation

Depyrogenation is the destruction or removal of bacterial endotoxins, which are found in the outer cell walls of Gram-negative bacteria and can cause a pyrogenic reaction in patients, such as fever, chills, hypotension, nausea or vomiting.

Depyrogenation is accomplished via dry heat or rinsing (see USP Chapter 797, Section 10.1). Steam heat cannot be used for depyrogenation because the temperatures are too low.

Dry heat depyrogenation is used for glassware, metal, and other thermostable containers or components and is accomplished through a dry heat oven. Depyrogenation requires much higher temperatures than those used for sterilization. Temperature and cycle time can vary, but a typical cycle is 250° for 30 minutes.

NEW The required dry heat depyrogenation cycle should be identified in the pharmacy's policies/procedures. Additionally, effectiveness of the dry heat depyrogenation cycle must be established by using endotoxin challenge vials (ECV) initially and annually thereafter *(New requirement; See USP Chapter 797, Section 10.1)*. ECVs are biological indicators that contain a known amount of bacterial endotoxins. The depyrogenation cycle is run with these vials present to verify that it can destroy the endotoxins.

For items that are not thermostable and cannot go through a dry heat cycle, depyrogenation must be accomplished by multiple rinses with sterile, non-pyrogenic water (e.g., sterile water for injection or irrigation). Items must then be thoroughly drained or dried immediately before use.

***See USP Chapter 1228 for more information on depyrogenation.*

## Compounding Records

Class H pharmacies must maintain a compounding log that complies with 20 CSR 2220-2.400 (Compounding Standards of Practice), or maintain a compounding record that complies with USP Chapter 797. [20 CSR 2220-2.200(5)(C)].

NEW Master formulation records (MFR) must also be maintained as required by USP Chapter 797. MFRs are essentially "recipes" that detail how the CSP is prepared and are required by USP Chapter 797 to be kept for all CSPs prepared from nonsterile ingredients or CSPs prepared for more than one patient (batches).

The chart below summarizes compounding record/log requirements under both USP Chapter 797 and 20 CSR 2220-2.400:

## Compounding Logs/Records

| *Type of record* | *20 CSR 2220-2.400 (Current)* | *Revised 2.200* |
|---|---|---|
| **Master Formulation Record** | • Not required, however, the method/procedure used to make the CSP must be documented (in compound log or pharmacy records ("e.g., recipe book")) | • Name, strength or activity, and dosage form of the CSP<br>• Identities and quantities of all ingredients, including individual characteristics<br>• Container closure system type and size<br>• Complete instructions for preparing the CSP, including any equipment/supplies, a description of compounding steps, and any special precautions.<br>• Physical description of the CSP's final form.<br>• BUD and storage requirements<br>• Reference or source used to support stability<br>• Any required quality control procedures required (e.g. pH testing, filter integrity testing)<br>• Any other information that may be needed to describe the compounding process and allow for replication (e.g., sterilization method, adjustment of tonicity or pH) |
| **Compounding Record/Log** | • The compounding method used (see master formulation record above)<br>• Compounding date;<br>• Identity of compounding pharmacist;<br>• List of drug products/ingredients and their amounts by weight or volume;<br>• Description of compounding process and, if necessary for proper compounding, the order of drug product/ingredient addition (e.g., recipe/formula cards); | • Name, strength or activity, and dosage form of the CSP<br>• Time and date of preparation of CSP<br>• Assigned internal serial number (e.g. lot number, prescription number)<br>  ○ Prescription number or unique identifier is required to track dispensing history of CSP<br>• Identification of individuals involved in both the compounding and verification process<br>• Name, weight or volume, and strength or activity of each component<br>• Vendor/manufacturer, lot number, and expiration date for each component of CSP prepared for more than one patient (as a batch) and for any CSPs prepared using nonsterile ingredients |

| *Type of record (Cont'd)* | *20 CSR 2220-2.400 (Cont'd) (Current)* | *Revised 2.200 (Cont'd)* |
|---|---|---|
| **Compounding Record/Log** | • Source, lot number and BUD of each drug product/ingredient, with an in-house lot number and BUD for bulk compounded preparations; and<br>• A prescription number or readily retrievable unique identifier. (Rx #s/Identifiers from a batch compound must be recorded individually). | • Total quantity compounded<br>• Final yield (e.g. quantity, number of containers, number of units) **Previously only required for risk level 3*<br>• Assigned BUD and storage requirements **Previously only required for batches*<br>• Results of any quality control procedures conducted (e.g. pH testing, filter integrity testing, visual inspection)<br>• If applicable:<br>  ○ MFR reference for the CSP<br>• Any calculations used to determine and verify any quantities and/or concentrations of components |

## Release Inspections and Testing

All final preparations must be inspected by a pharmacist to verify the CSP was compounded accurately. Additionally, a pharmacist must visually inspect finished CSPs before release for container closure integrity, visible particulates, or other foreign matter/visual defects. USP Chapter 797 includes enhanced release/testing requirements that are summarized below:

| *Inspections & Testing* | | |
|---|---|---|
| *Type* | *Previous 2.200* | *Revised 2.200* |
| **Visual inspection** | • Before use, ingredients and containers are inspected for:<br>  ○ Defects<br>  ○ Expiration date<br>  ○ Integrity<br>• Final preparation inspected for:<br>  ○ Clarity<br>  ○ Container leaks<br>  ○ Integrity<br>  ○ Appropriate solution cloudiness or phase separation<br>  ○ Color<br>  ○ Volume<br>  ○ Particulate and/or foreign matter<br>• Background light or other means for visual inspection required. | • Upon receipt, Ingredients and container closures inspected for:<br>  • Evidence of deterioration or unacceptable quality.<br>• Before use, ingredients and container closures inspected for:<br>  ○ Correct identity<br>  ○ Appropriate quality<br>  ○ Within expiry<br>  ○ Storage conditions were correct<br>  ○ Container breaks<br>  ○ Looseness of cap/closure<br>  ○ Deviations from expected appearance, aroma, or texture.<br>  ○ Sterile container closures are free from defects |

| *Inspections & Testing (Cont'd)* | | |
|---|---|---|
| *Type* | *Previous 2.200 (Cont'd)* | *Revised 2.200 (Cont'd)* |
| **Visual inspection** | *(See prior page)* | • CSP visually inspected for:<br>○ Physical appearance is as expected<br>○ Free of visible particulates or other foreign matter<br>○ Free of discoloration/defects<br>○ Container closure integrity including leakage, cracks, improper seals<br>○ Correct labeling<br>• If CSP is not released or dispensed on the day it's prepared, it must be inspected immediately before dispensing. |
| **Sterility testing** | • Not required for risk level 1 or 2.<br>• Required for all risk level 3 compounds according to USP Chapter 71 which includes method suitability testing.<br>• Minimum number of samples tested based on USP Chapter 71, Tables 2 & 3. | • Not required for category 1 CSPs.<br>• Required for:<br>1. Category 2 CSPs when a BUD is assigned that requires sterility testing (See USP Chapter 797, Table 13)<br>2. All category 3 CSPs<br>• Performed according to USP 71 or a validated alternative method.<br>• Minimum number of samples tested based on USP Chapter 71, Tables 2 & 3 with the following exception:<br>– If #1-39 CSPs are compounded, sterility testing must be performed on 10% of the number of CSPs prepared (rounded up to the next whole number.) |
| **Endotoxin testing** | • Not required for risk level 1 or 2.<br>• Required for all parenteral risk level 3 compounds according to USP Chapter 85 | • Not required for category 1 injectable CSPs<br>• Required for:<br>○ Cat. 2 injectable CSPs compounded from nonsterile components & assigned a BUD that requires sterility testing (see USP Chapter 797, Table 13)<br>○ Category 3 injectable CSPs that are compounded from one or more nonsterile components |

| *Inspections & Testing (Cont'd)* | | |
|---|---|---|
| *Type* | *Previous 2.200 (Cont'd)* | *Revised 2.200 (Cont'd)* |
| **Potency** | • Not required for risk level 1 or 2<br>• Required for risk level 3 CSPs assigned a BUD > 30 days (once per formulation)<br>• For nonsterile bulk active ingredients used in CSPs, a pre-release check of potency is required which includes a pharmacist checking:<br>  ○ Lot(s) of active ingredients have the proper labeling, potency, purity, COA and other relevant qualities<br>  ○ All weighing and measurements are correct<br>  ○ Fill volumes | • Not required for any Category CSP<br>• Not sufficient or allowed to be used to support BUDs assigned to Category 3 CSPs<br>• For nonsterile bulk active ingredients used in CSPs, a pre-release check of potency is required which includes a pharmacist checking:<br>  ○ Lot(s) of active ingredients have the proper labeling, potency, purity, COA and other relevant qualities<br>  ○ All weighing, calculations, and measurements are correct<br>  ○ Fill volumes |
| NEW NEW **Stability study** | • Not required | • Required for Category 3 CSPs (once per formulation)<br>• The BUD must be supported by data using a stability-indicating analytical method (e.g., forced degradation studies)<br>  ○ Study needs to quantify the amount of active ingredient from its degradants and impurities<br>  ○ Study must use the same container closure that will be used during compounding<br>  ○ To apply stability data, CSPs must be prepared according to the exact formulation and stored in a container closure of the same materials as in the study |
| **Particulate matter testing** | • Not required | • Required for injectable or ophthalmic Category 3 CSPs (once per formulation) |
| NEW **Container closure integrity** | • Not required | Required for:<br>• Multiple-dose CSPs (once per formulation)<br>• Category 3 CSPs (once per formulation and for each container closure system) |

| *Inspections & Testing (Cont'd)* | | |
|---|---|---|
| *Type* | *Previous 2.200 (Cont'd)* | *Revised 2.200 (Cont'd)* |
| **Antimicrobial effectiveness testing** | • Not required | Required for aqueous multiple-dose CSPs (once per formulation):<br>• Can rely on testing conducted by the pharmacy or published in peer-reviewed literature sources. If relying on literature, the formulation and container closure system must be the same<br>• Exceptions exist for multiple-dose, non-preserved, aqueous topical CSPs (See USP Chapter 797) |

NEW

All out-of-specification results must be investigated and include an investigation of potential causes, a corrective action plan, and documentation. For sterility test failures, the investigation must include identification of the microorganism and an assessment of whether the conditions that caused the sterility test failure may affect other CSPs.

Sterility testing of a CSP can provide additional assurance of the absence of contamination, however, **passing a sterility test does not guarantee that all units of the batch are sterile**. Contamination may not be uniformly distributed throughout the batch and therefore, may not be detected or present in the samples tested.

A CSP may be released for emergency dispensing pending test results, if approved by the prescriber. [20 CSR 2220-2.200(6)(B)] A separate authorization from the prescriber is required for each emergency dispensing. For purposes of 20 CSR 2220-2.200, emergency dispensing is defined as "*a situation where a preparation is necessary for immediate administration, and no alternative product or preparation is available*." All final preparations must be inspected by a pharmacist to verify that the preparation was compounded accurately. Documentation of dispensing, the prescriber's approval, and the emergency need must appear in the prescription record.

## Labeling

In addition to the prescription label requirements in § 338.059, the following chart compares the CSP labeling changes. ***Red italics*** signify changes:

[CONTINUED ON NEXT PAGE]

| CSP Label Requirements | |
|---|---|
| *Previous 2.200* | *Revised 2.200* |
| • Name and dosage of drug<br>• Beyond use date<br>• Storage requirements if stored at other than controlled room temperature<br>• Any device specific instructions<br>• Auxiliary labels, when applicable<br>• Designation of hazardous drugs when applicable<br>• Lot number for batched preparations | • Active drug and amount, activity, or concentration<br>• *Dosage form*<br>• *Amount or volume if not obvious from container*<br>• Beyond use date<br>• Storage requirements if stored at other than controlled room temperature<br>• Internal ID number (lot number, barcode, prescription)<br>• *"SDV" if space permits (single-dose vials)*<br>• *"MDV" if applicable (multi-dose vials)*<br>• Required if applicable:<br>  ○ Special handling instructions<br>  ○ *Route(s) of administration*<br>  ○ Warning statements** |

**USP Chapter 797 provides contact information for the compounding facility is only required if the CSP is "sent outside [the] facility or healthcare system." Section 338.059, RSMo, requires that all prescriptions contain the pharmacy's name and address; This requirement is statutory and has not been waived/modified.

## Category 3 CSPs

The following table contains additional requirements specific to Category 3 CSPs *(This list is not exhaustive; Other Board rule/USP Chapter 797 requirements apply)*:

| Category 3: Additional Requirements | |
|---|---|
| **Personnel** | • Sterile garb only, may not be reused<br>  ○ Applies to all personnel entering the buffer room where Category 3 CSPs are compounded; Always applies regardless of whether Category 3 CSPs are being compounded on a given day<br>• No skin exposure in buffer room<br>  ○ Applies to all personnel entering the buffer room where Category 3 CSPs are compounded; Always applies regardless of whether Category 3 CSPs are being compounded on a given day<br>• More frequent competency evaluations (every 3 months) for personnel who participate in or oversee the compounding of Category 3 CSPs |

| *Category 3: Additional Requirements (Cont'd)* | |
|---|---|
| **Environmental** | • More frequent sporicidal cleaning (weekly in most areas)<br>• More frequent surface sampling (weekly and PEC with each batch)<br>• More frequent air sampling (monthly)<br><br>**Environmental requirements apply to all classified areas where Category 3 CSPs are compounded at **all times**, even if Category 3 CSPs are not being compounded on a given day |
| **CSP Testing (Once per formulation and container)** | • Stability-indicating method study<br>• Particulate matter<br>  ○ Injections: USP <788><br>  ○ Ophthalmic solutions: USP <789><br>• Container closure-integrity test: UPS <1207> |
| **CSP Testing (Each batch)** | • Sterility test: USP <71> or validated alternative method<br>• Endotoxin test: Injectable CSPs if any nonsterile ingredients used |
| **Batch Size** | • Maximum: 250 units |

## Recalls

A recall must be initiated if a CSP is deemed to be misbranded, adulterated, or nonsterile, or if end preparation testing results are out of specification. [20 CSR 2220-2.020(9)] The following notifications must be made in the event of a recall:

- Prescriber: Must be notified of the nature of the recall, the identified problem(s) and any recommended actions
- Patient: Must receive the same notification as the prescriber if the preparation has the potential to harm the patient
- Board: Must be notified within 3 business days of the recall. [20 CSR 2220-2.020(9)]

## Commercially Available Products

As a reminder, 20 CSR 2220-2.400(9) prohibits licensees from compounding preparations that are commercially available or that are essentially copies of commercially available products (see exceptions below).

An “essential copy” of a commercially available product is defined in Missouri as a compounded preparation that has:

1. The same active pharmaceutical ingredient(s) as the commercially available drug product;
2. The same manner of administration as the commercially available drug product; and
3. The same, similar, or an “easily substitutable” dosage strength. “Easily substitutable” means the same or similar dosage strength can be achieved by administration of fractional or multiple doses of the commercially available drug product (e.g., 1ml of a compounded 120mg/ml vs. 1.2ml of a commercially available 100mg/ml product). [20 CSR 2220-2.400(9)(A)]

Licensees may only compound a commercially available product if:

1. The product is unavailable due to problems other than safety or effectiveness (e.g., on back order). The pharmacy must confirm and document that the commercially available product is not available despite due diligence. [20 CSR 2220-2.400(9)]. Examples would include documentation from the FDA Drug Shortage database or the manufacturer/distributor showing the dates the product was unavailable. Note: A drug on the FDA shortage list is not commercially unavailable if it can be reasonably procured from a manufacturer/distributor. **Licensees must stop compounding/ dispensing the preparation once the product becomes commercially available again;** or
2. The prescriber determines there is a “specific medical need” for a variation of a commercially available compound for an individual patient, or the prescriber determines a modification of the commercially available product would produce a clinically significant difference for the patient. [20 CSR 2220-2.400(9)]. The “specific medical need” is the medical reason why the commercially available product cannot be used. Cost or convenience are insufficient to show a “specific medical need.”

**A different formulation still counts as an essential copy of a commercially available product unless there is a documented specific medical need or clinically significant difference for the variation from the prescriber** (e.g., sesame seed oil vs. peanut oil).

- A prescription that only identifies a patient’s name and compounded preparation formulation is insufficient to support compounding a commercially available product.
- Prescriber documentation that only states that a specific medical need or clinically significant difference exists without identifying the specific need or difference for the patient is not considered sufficient.

Prescriber documentation for compounding a commercially available must be maintained must be maintained in the pharmacy’s records (e.g., on the prescription/in the patient’s profile). [20 CSR 2220-2.400(9)]. For verbal communications, the Board recommends documenting the name of the person verifying the medical need/clinically significant difference and the date.

## Quality Assurance/Quality Control

USP Chapter 797, Section 18 (Quality Assurance and Quality Control), requires that pharmacies maintain a written and documented quality assurance (QA) and quality control (QC) program to ensure that compounding consistently meets quality standards and ensure that CSPs meet specifications/requirements before release. The required QA/QC program must also include procedures for handling complaints.

As per USP Chapter 797, "designated person(s) responsible for the QA program must have the training, experience, responsibility, and authority to perform" assigned duties. The designated person must review the QA/QC program annually. Review results must be documented and appropriate corrective action taken when needed.

## Questions?

Questions regarding this Guidance or revised 20 CSR 2220-2.200 can be submitted to the Board office via e-mail: MissouriBOP@pr.mo.gov or by calling (573) 751-0091 *(e-mail is preferred)*.

Licensees can also submit an online question to a Board inspector on the Board's website or by scanning the below QR code. Questions received before 12 noon, Monday – Thursday, will receive a same day reply (excluding holidays/office closures):

Missouri licensees can also contact your Board Inspector. See the Board's Inspector County Assignments for Inspector contact information or scan the below QR code: